derivative thereof and analyzing the mixture of the candidate agent and human neutral sphingomyelinase or fragment or derivative thereof, wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent.

REMARKS

Claim 13 has been amended to recite use of a recombinant human neutral sphingomyelinase. The claim has been further amended to point out the analyzing step more specifically ie., by adding a step that compares enzyme activity in the presence and absence of the agent.

Support for the amendments can be found throughout the instant application including the Drawings and claims as filed originally.

Particular support for the recombinant enzyme of the claim can be found eg., under the Summary of the Invention. See pg. 3, lines 11-15 as an illustration.

Support for language adding the comparing step to claim 13 is found eg., at pg. 17, lines 8-10 as well as Example 2, specifically pg. 32, lines 10-14.

The amendment introduces no new matter to the application.

On pages 2-3 of the Office Action, claims 13-14 stand rejected under 35 USC §112, second paragraph as being indefinite. Although Applicants respectfully disagree with the rejection as formulated, grounds for it have been addressed by this submission. In particular, the language suggested by the Examiner has been adopted.

Claims 13, and 15-17 stand rejected under 35 USC §112, first paragraph as not being enabling for a method of identifying a compound including use of any human neutral sphingomyelinase fragment or derivative. Specifically, at pages 4-5, the Action contends that the specification fails to show what regions of the sphingomyelinase are needed for activity and how one would modify the protein. Applicants respectfully disagree.

The invention of claims 13 and 15-17 is a method of identifying a compound useful in the treatment or diagnosis of a specific condition ie., a human neutral sphingomyelinase (N-Smase) related disorder. Applicants agree with the Examiner that the application is enabling for use of native enzyme in the method. However, Applicants cannot agree that the claims should recite only that enzyme and not other related N-Smases.

For example, and as the specification makes clear, practice of the invention is not limited to any particular N-Smase so long as it can provide acceptable function. See eg., pg. 15, lines 25-29 ; pg. 16, lines 4-15; and pg. 17, lines 8-10 (disclosing particular invention methods in which suitable enzyme fragments or derivatives are used).

Specific examples of such acceptable N-Smases are disclosed throughout the present application. For example, pg. 7, lines 19-26 and Figures 1 and 2 disclose physical characteristics of the preferred native enzyme. Additionally suitable enzyme fragments or derivatives provide good activity in the standard activity gel assays as discussed eg., at pg. 8, lines 16-23. Preferred activity ranges in the assay have also been provided. Moreover, N-Smase fragments or derivatives with particular amino acid substitutions are disclosed at pg. 9, lines 1-20, for example. Nucleic acids that encode such suitable N-Smases are provided at pg. 10, lines 12-24. Nucleic acids having preferred basepair sizes and N-Smases having desired functional domains are provided at pg. 10, line 12 to pg. 11, line 4. Suitable enzyme isoforms are taught at pg. 11, lines 21-25.

As understood, the rejection takes the position that notwithstanding Applicants' disclosure of many specific N-Smases suitable for use with the claimed invention, use of anything but the native enzyme is not enabled on grounds that it would require undue experimentation to make and use the N-Smases. Applicants respectfully disagree.

The specification provides examples of suitable N-Smases for use with the claimed invention including, but not limited to, the native enzyme. Should use of a particular enzyme fragment or derivative be needed in a specific invention embodiment, the specification provides more than ample guidance about selecting an appropriate fragment or derivative.

For example, preferred N-Smases including the native enzyme as well as fragments or derivatives thereof, exhibit good activity in the activity assay using ^{14}C-sphingomyelin and N-Smase peptide. See pg. 8, lines 16-23; and Example 6.

Moreover, the chemical structure of the native N-Smase has disclosed both at the amino acid and nucleic acid levels. See Figures 1 and 2, for example. Important function domains in the structure are recognized. See pgs. 10-11, for example. Methods for producing suitable N-Smases, preferably by use of conventional recombinant means have been disclosed. See pg. 11, line 27 to pg. 12, line 10.

Accordingly, it is believed that any testing needed to identify or confirm suitable N-Smases for use with the claimed invention is well within the level of experimentation permitted by the Federal Circuit. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Applicants disagree with the rejection on other grounds.

For example, a worker in this field would be able to use the guidance provided by the instant disclosure to select appropriate N-Smases. Any inoperable embodiments of the type described by the rejection could be readily avoided. As described by the Court of Customs and Appeals:

> [M]any patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit 'factors which must be presumed to be within the level of ordinary skill in the art.' ... There is nothing wrong with this so long as it would be obvious to one of skill in the art how to include these factors in such manner as to make the embodiment operative rather than inoperative. *In re Cook and Merigold*, 169 USPQ 299, 302 (C.C.P.A. 1971) (quoting *In re Skrivan*, 166 USPQ 85, 88 (C.C.P.A. 1970)).

Thus, one of skill having read Applicants' disclosure would know to identify suitable N-Smases in addition to the native enzyme. Even if one assumes, *arguendo*, that a particular N-Smase fragment or derivative did not exhibit acceptable activity, that result, by itself, would not support the present enablement rejection. The worker would understand that another fragment or derivative as provided by the specification, could be tested and identified for suitable activity. The rejection has not provided any reason to doubt that the guidance provided by Applicants' disclosure could not be used to identify a range of acceptable N-Smases for use with the claimed methods.

It is noted that the rejection seems premised on the position that only claims drawn to exemplified invention embodiments satisfy the requirements of Section 112, first paragraph, notwithstanding the broader invention Applicants disclose.

Respectfully, such a position conflicts with established patent law. It is well-recognized that a patentee's invention is properly broader than specific embodiments identified in an application. Thus in *In re Anderson*, the CCPA reversed a rejection under Section 112, first paragraph and noted in particular (176 USPQ at 333):

> What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. **This it may not do**.... There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. (emphasis added).

Here, the claimed invention is broader than use of the native N-Smase singled-out in the rejection. As taught throughout Applicant's disclosure, the invention is compatible with a variety of suitable N-Smases including specified fragments and derivatives thereof.

In view of the guidance provided by the specification and applicable patent law, the information related at pgs. 4-5 of the rejection and particularly items A-D at pg 5 as supporting the present rejection is simply not needed to practice the invention as claimed.

Finally, it is noted that the Office has acknowledged the high level of knowledge in the art of enzymology. Office Action at pg. 8. Such knowledge is presumed to include information about N-Smase as well as acceptable fragments and derivatives of that enzyme.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 13 and 15-17 were rejected under 35 USC §112, first paragraph as containing subject matter which was not described in the specification so as to convey to one working in this field that Applicant had possession of the claimed invention when this case was filed. Applicant cannot agree.

As understood, basis for the rejection requires Applicant to provide information about the structure of N-Smase mutants and function of those mutants. See pg. 6 of the rejection. Respectfully, such information is not needed to practice the invention as claimed.

As discussed above, Applicant's disclosure provides ample description regarding how to make and use a variety of suitable N-Smases as well as acceptable derivatives and fragments thereof. That disclosure describes how to make and test N-Smases for use with the invention including the native enzyme. That description provides more than enough guidance to use not only the native enzyme but to select and use appropriate fragments and derivatives. The information required by the rejection is not needed to practice the information nor is it required by statute for reasons already mentioned.

In view thereof, reconsideration and withdrawal of the rejection are requested.

At pages 7-8 of the Action, claims 13-17 stand rejected as being obvious in view of Chatterjee (J. Biol. Chem. 264: 12554) and Ogita (WO/9518119). Although Applicants respectfully disagree, grounds for the rejection have been addressed by this submission.

In particular, claim 13 has been amended to recite a recombinant human neutral sphingomyelinase. As cited, none of the references taken individually or in combination provide for use of such an enzyme in any assay. In contrast, the claimed invention features recombinant enzyme for use in assays to detect agents that modulate N-Smase activity.

Applicant disagrees with the rejection on further grounds.

For example, as relied on, Ogita et al. disclose sphingomyelinase inhibitors. However, there is no disclosure in the reference that any of the cited inhibitors would impact the human neutral sphingomyelinase of the claimed invention. In contrast, the claimed invention selects for compounds that specifically modulate the human enzyme.

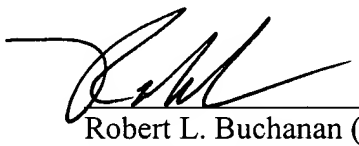
In view thereof, reconsideration and withdrawal of the rejection are requested.

Early consideration and allowance of the application are earnestly solicited.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

Respectfully submitted,



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Date: April 25, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 13 has been amended as follows:

13. (Amended) A method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder, comprising contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase or fragment or derivative thereof and analyzing the mixture of the candidate agent and human neutral sphingomyelinase or fragment or derivative thereof, wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent.

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